REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
17/09/07	research	2006-2007

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Rheoencephalogram Reflects Cerebral Blood Flow Autoregulation In Pigs	
	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	**5d. PROJECT NUMBER**
Michael Bodo, Frederick Pearce, Stephen Van Albert, Rocco Armonda	
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
Walter Reed Army Institute of Research, 503 R. Grant Ave, Silver Spring, MD; Cerebrovascular Surgery and Interventional Neuroradiology, Neurocritical Care National Naval Medical Center, Bethesda, MD and Walter Reed Army Medical Center, Washington, DC.	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	**10. SPONSOR/MONITOR'S ACRONYM(S)**
U.S. Army Medical Research and Materiel Command Combat Casualty Care (RAD II) 504 Scott Street Fort Detrick, MD 21702-5012 Combat Casualty Care Research Program	US Army MRMC CCCRP
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT

Hermann Scharfetter, Robert Merva (Eds.): ICEBI 2007, IFMBE Proceedings 17, pp. 695–698, 2007
www.springerlink.com © Springer-Verlag Berlin Heidelberg 2007

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The objective of the present study was to compare systemic arterial pressure (SAP), rheoencephalogram (REG), and carotid flow (CF) measured by Doppler ultrasound. Twenty-eight anesthetized Yorkshire pigs were measured to evaluate Cerebral Blood Flow (CBF) Autoregulation (AR) during several CBF manipulations: hemorrhage, positive end-expiratory pressure (PEEP), and transitory SAP decrease and increase. Data were sampled with 200 Hz and processed off-line. 1) Hemorrhage elicited a decrease in SAP and transitory increases in REG and CF amplitude; 2) PEEP resulted in a decrease in SAP and increases in REG and CF amplitude; 3) PEEP after hemorrhage caused decreases in SAP, REG and CF amplitudes. When CBF AR was present, it was detected by both REG and carotid flow. Following hemorrhage, CBF AR was lost; CF and REG passively followed SAP. The clinical importance of these findings is that REG can be measured more conveniently and continuously in humans than can Doppler ultrasound. Therefore, measurement of CBF autoregulation by REG has potential for use as a life sign monitoring modality.

15. SUBJECT TERMS

Cerebral blood flow, autoregulation, carotid flow, rheoencephalogram, pig

16. SECURITY CLASSIFICATION OF: a. REPORT	b. ABSTRACT	c. THIS PAGE	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
U	U	U	UU	4	Michael Bodo, MD, PhD.
					19b. TELEPHONE NUMBER *(Include area code)* 301 319 990

Icebi 2007

13th International Conference on Electrical Bioimpedance and the 8th Conference on Electrical Impedance Tomography

August 29th – September 2nd, 2007, Graz, Austria

Content:

Springer

International Federation for Biomedical Engineering (IFMBE)

Rheoencephalogram Reflects Cerebral Blood Flow Autoregulation In Pigs

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Abstract — **Cerebral blood flow autoregulation (CBF AR) is the phenomenon that makes blood flow constant within a physiological range regardless of blood pressure variations. When systemic arterial pressure (SAP) increases, vasoconstriction is taking place in the brain. The objective of the present study was to compare SAP, rheoencephalogram (REG), and carotid flow (CF) measured by Doppler ultrasound. Twenty-eight anesthetized Yorkshire pigs were measured to evaluate CBF AR during several CBF manipulations: haemorrhage, positive end-expiratory pressure (PEEP), and transitory SAP decrease and increase. Data were sampled with 200 Hz and processed off-line. 1) Haemorrhage elicited a decrease in SAP and transitory increases in REG and CF amplitude; 2) PEEP resulted in a decrease in SAP and increases in REG and CF amplitude; 3) PEEP after haemorrhage caused decreases in SAP, REG and CF amplitudes. When CBF AR was present, it was detected by both REG and carotid flow. Following haemorrhage, CBF AR was lost; CF and REG passively followed SAP. The clinical importance of these findings is that REG can be measured more conveniently and continuously in humans than can Doppler ultrasound. Therefore, measurement of CBF autoregulation by REG has potential for use as a life sign monitoring modality.**

Keywords — **Cerebral blood flow, autoregulation, carotid flow, rheoencephalogram, pig.**

I. Introduction

CBF Autoregulation

In the brain, cerebral blood flow (CBF), metabolism, and function are strongly interrelated. Although the mechanism of this complex system is not well known, there is satisfactory scientific and clinical evidence supporting the use of CBF autoregulation (AR = cerebrovascular reactivity) for diagnostic monitoring purposes. CBF AR is defined as the phenomenon that makes blood flow constant despite variations in blood pressure [1, 2]. Cerebral vascular resistance varies in response to variations in arterial pressure. The blood vessels (arteriola) in the brain constrict or dilate in response to changes in blood pressure between about 50 to 150 mmHg systemic arterial pressure (SAP). Below and above this limit or in pathological cases, CBF passively follows systemic arterial pressure.

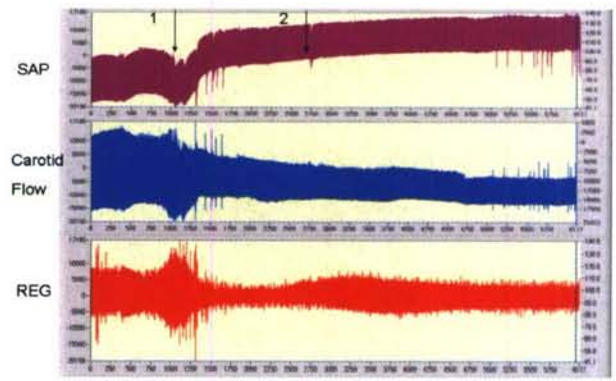

Fig.1 Cerebral blood flow autoregulation: following a transient decrease in SAP (arrow 1), CF and REG amplitudes transiently increased. During SAP increase, CF and REG amplitudes decreased. Events are indicated by arrows: Isoflurane off - Propofol/Ketamin start (1); start of ventilator (2). REG: filtered signal. Pig 12-05-06, fil: 10-14; Time window: 101.95 min.

REG (rheoencephalogram)

The physical basis of REG is the difference of electrical conductivity among tissues: cerebrospinal fluid and blood are better conductors than brain tissue. Consequently any change in fluid content within the cranial cavity will cause a change in conductivity/impedance. In healthy subjects, changes in the REG pulse wave reflect heart and respiratory activity as well as brain vasoconstriction and vasodilatation. Pathological conditions in the brain typically involve changes in fluid content caused by bleeding, vascular reaction, cerebral volume changes and vessel wall hardening, which is caused by arteriosclerosis. At the same time, these changes can cause an increase in intracranial pressure (ICP) and a resulting decrease in CBF. In studies of REG conducted in the early 1960s, REG was determined to be useful for monitoring ICP and arteriosclerosis [3].

The US Food and Drug Administration defined REG as follows: "A rheoencephalograph is a device used to estimate a patient's cerebral circulation using the electrical impedance method, with direct electrical connections to the scalp or neck area" [4]. The advantages of using REG for monitoring are that REG is non-invasive and continuous, and it provides an optimal indicator of CBF autoregulation. The disadvantage of REG as well as laser Doppler flow-

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metry has been that neither measures CBF in absolute units. However, the development of electronics and computation that has occurred since the 1960s now allows online calculation of REG derivatives.

The objective of the present study was to compare SAP, REG, and carotid flow (CF).

II. Methods

CBF AR responses of 42 anesthetized Yorkshire pigs were evaluated during several CBF manipulations: haemorrhage, positive end-expiratory pressure (in PEEP group only), and transitory SAP decrease and increase. Pigs were anesthetized with isoflurane and propofol/ketamin anaesthesia. The animals were monitored both with a bispectral index (BIS) device (A-2000, Aspect Medical Systems, Newton, MA) and with an anaesthesia monitor (isoflurane, O_2, CO_2) with RGM 5250 (Datex - Ohmeda, Louisville, CO). CBF AR was evaluated first by visual inspection of traces to establish the presence of CBF AR. In the PEEP group, 13 pigs were measured. In the cases of SAP and CF traces, AR was evaluated only by visual analysis; some recordings offered more than one CBF AR response; therefore, in total 18 records were compared within this group. Haemorrhage and transitory SAP changes were evaluated as CBF manipulation in both subgroups. In the COMP group ("complement activation"), 33 pigs were measured; few were excluded because of missing CF, REG or artefact-contaminated recordings; CBF AR response used for statistical evaluation was performed in 25 cases.

SAP was measured with a Microtip disposable pressure transducer inserted into the femoral artery, with a transducer control unit (Millar Instruments, Houston, TX), and with a Digi-Med Blood Pressure Analyzer, (Micro-Med, Louisville, KY). CF was measured on the right carotid artery with T201 ultrasonic blood flow meter (Transonic Systems, Ithaca, NY). REG was measured with a KR-Ea RHEO Preamp (45 kHz; Galileo, Italy), a bipolar system. Two electrodes were made from stainless steel (40 mm in length) and implanted into the brain via a burred hole (about 10 mm parasagittaly on the right side; inter-electrode distance of 10-20 mm) above and below the fronto-parietal sutura. Electrodes were fixed to the skull with Vetbond tissue adhesive (3M, St. Paul, MN) and instant adhesive 454 (Loctite, Hartford, CT). Average inter-electrode resistance was 1.9 ohm +/- 0.55 (n = 25).

Data were sampled with 200 Hz analogue digital conversion rate using DASH-18 (Astro-Med, (West Warwick, RI) and with a Dell PC equipped with an analogue digital converter card (PCI 6052E, National Instruments, Austin, TX); both analogue digital cards had 16 bit resolution. In the PC, DataLyser software (Baranyi) was used for recording. Data were processed off-line.

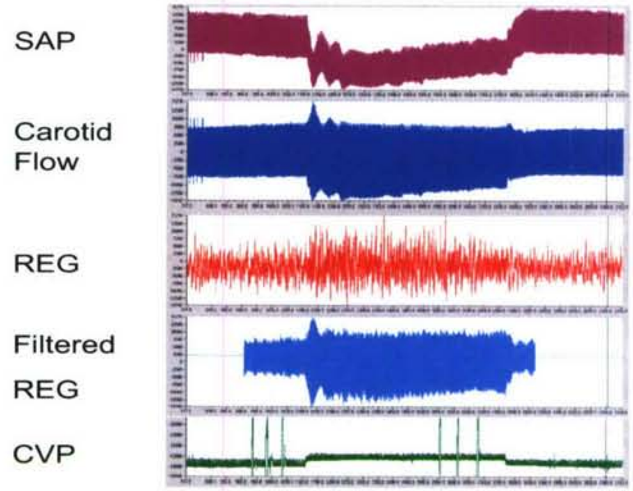

Fig.2. The effect of PEEP on CBF with intact AR. SAP decrease was elicited by PEEP with 20 water cm pressure. CF and REG amplitude increased. CVP: central venous pressure. Pig (PEEP 12) Propofol/Ketamin anesthesia; time window: 1435 sec; file 13-37 (717.5-2152.6 s).

Data processing involved measurement of 30 second traces (6000 data points) of SAP, CF and REG using DataLyser. DataLyser is based upon LabVIEW software (National Instruments, Austin, TX) specifically developed to display, store and quantify analogue physiological signals. In the PEEP group, REG was filtered with 0.5 - 100 Hz, Butterworth, 512 points, order: 5, attenuation: 40 dB.

Mean values of SAP, standard deviation of CF and REG signals were used for statistical comparison. The control samples were taken from each modality before SAP change. The CBF AR sample was taken at the time of maximal response in REG and CF. Data were exported into an Excel (Microsoft, Redmond, WA) spreadsheet for further processing. Percentage change between control and CBF AR maximum was used to compare SAP, CF and REG to each other. Paired Student's t-test was used for statistical comparison. P value less than 0.05 was considered significant.

III. Results

In the PEEP group, 60 CBF AR responses were observed, covering SAP increases and decreases, haemorrhage and transitory SAP changes.

Comparison between the PEEP and the COMP groups showed a significant difference in percentage changes in only one case: REG ($p > 0.0001$) (see Table 1). When CBF AR was present in both groups, it was detected by both REG and carotid flow. Following haemorrhage, CBF AR was lost; CF and REG passively followed SAP.

Table 1. Summary of percentage changes. SD: standard deviation; P: probability; groups: P calculation among groups

	SAP	CF	REG
	PEEP	Group (n=17)	
Mean	43.93	108.91	253.23
SD	10.51	61.12	190.26
P	0.0001	0.0022	0.0001
Groups	SAP-CF	CF-REG	SAP-REG
	COMP	Group (n=25)	
Mean	39.69	88.17	64.11
SD	16.66	70.32	61.34
P	0.0005	0.1	0.06
Groups	SAP-CF	CF-REG	SAP-REG
	PEEP - COMP Group Comparison		
P	0.3	0.3	0.0001
Groups	SAP-SAP	CF-CF	REG-REG

In the PEEP group there were significant changes among SAP, CF and REG. These results were partly caused by higher REG values, caused by filtering of the REG signal; similarly, a significant difference in REG values was observed between the PEEP and COMP groups (see Table 1).

CBF AR was not related to CO_2 alteration, as shown by simultaneously the recorded CO_2 trace.

IV. Discussion

The advantage of REG monitoring is that it is continuous and non-invasive. The drawback is that no clear pathophysiological background is known to have multiple influencing factors. An extensive overview of such influencing factors was beyond the scope of the present study but was detailed previously by Moskalenko and Jenkner [5,6].

Clinical considerations

The ultimate goal of our work is to develop a vital sign monitor using REG. Such a device would be useful in neurosurgery intensive care units (NICU). Typically, CBF is monitored in NICU once a day by Doppler ultrasound, which in this case measures CBF on the middle cerebral artery; however, this measurement is not a continuous procedure. The probability of detecting vasospasm in recent clinical practice is low, although such a capability would be lifesaving [7]. Once its diagnostic potential and limitations have been established, REG has the potential to be an optimal CBF AR monitoring modality.

The necessity of using a continuous non-invasive CBF monitor is that the traditional vital sign monitors used in the NICU are not sufficient. Such monitors measure cardiorespiratory modalities but not brain-related ones. For example, during elevation of intracranial pressure, which is a potential risk in many patients, signs of increased ICP are hypertension, bradycardia, and irregular respiration (the "Cushing response"). In this case, the SAP value alone can be misleading for the hypotensive patient.

PEEP is used clinically to increase the percentage of saturation in red blood cells by retaining air in the lungs for an increased period of time. Here we observed that PEEP, in combination with hypotension, causes decreased CBF (loss of CBF AR) and with potential for unwanted neurological complications in human neurosurgical patients.

REG Signal Processing

All stored records that showed changes in SAP, CF and REG were available for visual evaluation. Although the qualitative summary involved other pigs, the statistical evaluation included only those pigs with SAP, CF and REG traces (PEEP: 17 + COMP: 25=42). Also, a single pig may have been used in more than one sample.

The main problem in using REG for vital sign monitoring is the need to clean the REG signal from various artefacts and to identify the pathophysiologic background of alterations in the REG pulse wave. Biological artefacts include the following: 1) respiration (a subharmonic with the alternating frequency of respiration); 2) M-wave (a subharmonic of 3-9 oscillations per minute) [8], which is the result of a sympathetic influence on SAP; and 3) a reflection of changes in ICP [3,9]. Artefacts 1 and 2 were successfully decreased by used a filtering method.

A bipolar REG signal contains only the AC (pulsatile) component of the electrical resistance between two electrodes, which is about 5 percent or less of the total resistance [10]. Additionally, REG is a biphasic signal; consequently, its amplitude change as relevant biological information can not be processed with a simple reading and summarizing of the minimum – maximum distance of a pulse curve. The same problem occurs during calculation of the REG pulse integral; in both cases, negative numbers will be subtracted.

We also analyzed REG by means of the amplitude histogram method; the respiratory and other sub-harmonics caused misleading information, often resulting in much larger values than the REG pulse itself. In the case of our REG signals, the FFT showed a dominant frequency of 0.1 Hz. The high pass filtering method used in the PEEP group decreased the amplitude of unwanted sub-harmonics caused by respiration and M waves and also caused a phase shift and a pulse distortion, making the REG signal unavailable for use in further analysis. Additional REG signal processing was detailed previously [11, 12].

Anatomical background and anaesthesia

Anatomical background. The known discrepancy in the correlation between carotid flow and REG has a recognized anatomical cause. It was previously described that the involvement of a vessel in CBF AR is size-dependent: larger arteries are less involved than arteriola [13]. Consequently, the arteriolar change observed in brain by REG reflects arteriolar function more than it reflects functions in larger arteries (e.g. carotid).

Anaesthesia. Although anaesthesia was controlled by BIS monitoring, the transition between the two types of anaesthesia was not uniform. However, CBF measurement was not the main purpose of these experiments and provided only a peripheral variable, which served as a useful index of the maintenance of physiological responsiveness within the range of CBF AR.

V. Conclusions

The novelty of this work is that the correlation demonstrated between CBF and REG amplitude is comparable to that obtained by means of carotid flow, the accepted gold standard of CBF. Prior to this study, the standard deviation of REG pulse amplitude was not used to characterize CBF AR. The use of standard deviation of REG amplitude proved to be a useful variable in handling the biphasic REG signal in which case the negative values could not be calculated. Additionally, an improved signal-to-noise ratio was achieved by use of filtering.

This study shows that REG has potential for use as a non-invasive brain monitoring modality, with applications as both a field neuro-rescue device [7] and as an endpoint for resuscitation efforts.

Human and animal studies are in progress to find correlation with quantitative brain tissue perfusion during various CBF manipulations.

Acknowledgment

The authors thank S. Alexander, L. Tabaku, A. Garcia, R, Peckham, P. Quinn, D. Rayburn, T. Settle, C. Morrissette for their contribution; J. Andrist, A. Battles, C. Bergman, A. Hamilton, C. Hite, J. Hunt, R. Martinez, M. Negron, S. Nena, M. Repetto, T. Webster for their technical assistance; L. Baranyi for DataLyser; and Janice Meer for assistance with the manuscript.

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